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Article type : Letter to the Editor

The relationship of habitual diet with oesophageal inflammation and integrity in Eosinophilic Esophagitis

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Key words:

Adults, habitual dietary intake, esophageal mucosal integrity, Eosinophilic Esophagitis, inflammation.

To the editor:

The prevalence of Eosinophilic esophagitis (EoE), affecting both adults and children, has strongly increased in recent years for reasons currently unknown. It is characterised by inflammation of the esophagus, dysphagia and food impaction, and is a relatively new chronic immune-mediated manifestation within the spectrum of allergic diseases. We hypothesized that the habitual diet composition is a risk factor of the development and/or persistence of EoE, as nutrition can, either favorably or unfavorably, influence mucosal integrity and tolerance, local and systemic immune function, the oral and intestinal microbiome (and therefore probably also the esophageal microbiome)(1), and epigenetics. Immunomodulatory effects are known for certain fibers, fats, proteins, iron, zinc, copper, selenium, vitamins A, C, D, B6 and B12, omega 3 and 6 fatty acids and folate (2-4). Thus, nutrition may have an allergy-protective or allergy-provoking effect. However, no studies have been published yet on the habitual dietary intake in EoE patients. This study is the first reporting the relationship between habitual dietary intake in adult EoE patients, before starting any (elimination) diet other than self-imposed dietary measures, and esophageal inflammation and mucosal integrity. Our *aims* were to assess in adult EoE patients (1) the relationships of the habitual dietary intake with esophageal eosinophilic inflammation and mucosal integrity, and (2) the dietary intake in those patients with active disease compared to those in remission.

Our study had a cross-sectional design and was carried out in adult patients, previously diagnosed with EoE (≥ 15 eosinophils/high power field (HPF) and symptoms of esophageal dysfunction) after inclusion in two different studies in 2013-2015 (Trialregister.nl NTR4052 and NTR4892) in the Academic Medical Center, Amsterdam, the Netherlands. We used the data collected at baseline (6,7) in 34 patients, including five patients who did not receive the intended treatment because of histologic remission assessed at baseline, after inclusion. Until this baseline assessment, the included EoE patients of these studies had no dietary intervention other than self-imposed dietary measures. All patients stopped the intake of steroids, leukotriene inhibitors, monoclonal antibodies anticoagulants, NSAIDs at least 8 weeks prior to the study. If necessary, continuation of proton pump inhibition in stable dosage was allowed. At baseline, habitual dietary intake, esophageal inflammation and mucosal integrity were assessed. No dietary analyses were performed during or after dietary intervention.

Oesophageal inflammation was measured by peak eosinophil counts/HPF, and integrity by Electrical Tissue Impedance Spectroscopy (ETIS), transepithelial resistance (TER) and transepithelial flux of fluorescein and rhodamine. See online supporting information (Boxes 1 and 2), for more details on these measurements.

Patient characteristics are described in Table 1. Table 2 shows that in the multiple regression analyses the following nutrients or food groups had a statistically significant negative (favorable) relationship with eosinophil counts: the amount of dietary fiber ($\beta = -0.443$; $p = 0.044$), iron ($\beta = -0.656$; $p = 0.001$), rice/pasta instead of potatoes ($\beta = -0.361$; $p = 0.028$) and soy products ($\beta = -0.450$; $p = 0.007$). In contrast, the amount of dietary phosphorus ($\beta = 0.659$; $p = 0.001$) had a significantly positive (unfavorable) relationship with eosinophil counts. As compared to patients with active disease (≥ 15 eosinophils/HPF) ($n = 29$), patients in remission consumed statistically significantly more fiber ($p = 0.012$), magnesium ($p = 0.024$), folate ($p = 0.002$), vegetables ($p = 0.025$), yoghurt ($p = 0.021$) and soy ($p = 0.037$) (Mann Whitney test). Additionally, patients in disease remission consumed statistically significantly less vitamin B12 ($p = 0.006$) and meat ($p = 0.034$) than patients with active disease. Median amounts of these nutrients/foods consumed by the two groups of patients are presented in Table S1 in the online supporting information. It is unlikely that differences in disease activity between the two groups could be explained by food avoidance in the group in remission, because in this group dietary elimination was very limited.

Multiple regression analyses also revealed that, in patients with active disease, the intake of sunflower oil and/or stir fry oil was negatively (i.e. unfavorably) related to values of TER ($\beta = -0.499$; $p = 0.019$). The consumption of buttermilk/LGG yoghurt drink had a statistically negative (i.e. favorable) relationship with values of fluorescein flux ($\beta = -0.716$; $p = 0.002$), while the amount of added fat was positively (unfavorably) related to fluorescein flux ($\beta = 0.624$; $p = 0.012$). Moreover, the amount of dairy was negatively (favorably) related to rhodamine flux ($\beta = -0.566$; $p = 0.015$), while the amount of sunflower oil or stir fry oil ($\beta = 0.735$; $p < 0.001$) was positively (unfavorably) related to rhodamine flux.

Our findings show that dietary factors may either favorably or unfavorably impact inflammation and mucosal integrity of the esophagus. With respect to these health outcomes, high intake of dietary fibre, iron, fermented dairy (buttermilk, LGG yoghurt drink), dairy, pasta/rice and soy may be favorable, while high intake of omega-6 rich oil (sunflower oil/stir fry oil), total added fat and phosphorus (abundant in animal-based foods) may be unfavorable.

Remarkably, different nutrients/foods were significantly related to different outcomes. However, different types of fat or fatty acids (total added fat, linoleic acid and sunflower oil/stir fry oil) all showed unfavorable relationships with one or more *in vitro* permeability tests (TER, Fluorescein and Rhodamine flux).

Generally, we found weak or moderate relationships with the outcome measures. However, the relationship of all ingredients of the total diet together may be stronger related to these outcomes, because of cumulative, synergistic or interactive effects.

(8).

Our study design does not allow for conclusions on causal relationships and the results should be interpreted with caution. However, our hypothesis that the habitual diet composition is a risk factor for the development and/or maintenance of EoE seems promising because the found relationships (or trends) are in line with general concepts of a healthy (immune-enhancing and anti-inflammatory) diet, or, in contrast, unhealthy (immune-suppressive and pro-inflammatory) diet:

1. Fiber, iron and vitamin A are known for their beneficial effects on the intestinal microbiome, the maintenance of mucosal integrity (2-5) and their anti-inflammatory effects in asthma (9);
2. Omega-6 fatty acids (in sunflower oil/stir fry oil), linoleic acid and high total fat intake are known for their pro-inflammatory and (epi)genetic effects (5,10);
3. Consumption of buttermilk/ LGG drink yoghurt and dairy all fit in the concept of a healthy diet, rich in nutrient dense and fermented foods (4,5);
4. High intakes of protein, meat/meat products, vitamin B12 and phosphorus are provided by animal-based foods, that might be therefore be determined as unfavourable, but not meaning that e.g. protein and vitamin B12 per se are unhealthy, whereas high intakes of dietary fiber, magnesium, potassium and soy products are provided by plant-based foods that might be considered as favorable related to EoE pathogenesis (4,5).

It seems contradictory that we found protective effects for soy and dairy, while soy and dairy are common triggers in EoE. We hypothesize that the protective effects of dairy might be contributed to fermented dairy and/or full fat dairy (rich in vitamin A) as long as the disease has not yet developed. The protective effect of soy could be explained by the plant-based origin of soy. Once EoE has developed and permeability has increased, T-cell mediated reactions are induced to these commonly consumed foods.

Strengths of our study are the well-characterized study population and the use of a detailed, standardized way of diet history taking. Limitations of this study are the cross-sectional design, the relatively small study population. In addition, the study design did not allow us to identify the culprit food allergens in all patients because study NTR4052 was stopped preliminary. Because of the hypothesis-generating character of our study, we did not correct for multiple testing. However, when verifying the direction (favorable or unfavorable) of the non-significant effects of the nutrients/foods in Table 2 for the other outcome variables, the directions of 71% of relationships point at the same direction, yielding the most consistent results for high intake of protein and meat/meat products (unfavorable) and fiber (favorable) (see online supporting information Table S2). Finally, we were not able to calculate the quantitative intake of dietary supplements, because of the inconsistent use of amounts and types of supplements by patients.

If our hypothesis will be confirmed in prospective or intervention studies, there may be a role for an immune-enhancing and anti-inflammatory diet, to be encouraged and facilitated from a very young age, in the prevention and, in addition to elimination diets, also in the treatment of EoE.

Conflicts of interests

Marleen van Ampting, Lucien Harthoorn and Simone Eussen are employed by Nutricia Research BV, but declare that they were not affected by this affiliation in performing this study. The other authors declare that they do not have any conflicts of interest that may be inherent in this submission.

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Contribution of each author

Berber Vlieg-Boerstra conceived the presented concept. Marlou de Kroon and Berber Vlieg-Boerstra were responsible of the study design, performed the statistical analyses and wrote the first draft of the paper. All authors critically revised the final manuscript.

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Table 1. Patient characteristics of EoE patients (n=34) at baseline

	<i>n/N (%), or median; IQR</i>
Gender; males (n/N; %)	26/34 (77)
Age in years: median; IQR (n=34)	45.2; 29.0-49.3
BMI (kg/m ²), median; IQR(n=34)	24.7; 21.0-26.6
Atopic disease in % (n=34)	27/34 (79)
- Atopic dermatitis	7/34 (21)
- Asthma	14/34 (41)
- Allergic rhinitis	17/34 (50)
- Food allergy	21/34 (62)
- of which oral allergy symptoms	17/34 (50)
Food avoidance in % (n=34)	
<i>Food groups avoided because of OAS, food allergy or EoE</i>	19/34 (56)
<i>Food groups avoided because of OAS:</i>	12/34 (35)
- one or more types of fruit	2/34 (6)
- one or more types of nuts/peanut/seeds/ legumes	2/34 (6)
- one or more types of fruits/vegetables and nuts/peanut/ seeds/legumes	8/34 (24)
<i>Food groups avoided because of other food allergy:</i>	
- one or more types of fruits/vegetables	7/34 (21)
- one or more types of nuts/peanut/seeds	3/34 (9)
- fish	3/34 (9)
- buckwheat	1/34 (3)
- cow's milk	1/34 (3)
<i>Food groups avoided because of EoE (dysphagia, impaction or dyspepsia):</i>	1/34 (3)
- one or more types of nuts/peanut/seeds	12/34 (35)
- one or more types of fruits/vegetables	7/34 (21)
- alcoholic beverages	7/34 (21)
- dairy	5/34 (15)
- meat	3/34 (9)
- fish	3/34 (9)
- egg	2/34 (6)
- gluten	2/34 (6)
- bread	2/34 (6)
	1/34 (3)
Supplements % (n=34)	
- taken on a regular base	8/34 (23)
- taken on an irregular base	2/34 (6)
- no supplements	20/34 (59)
- unknown or unclear	4/34 (12)
<i>Baseline measures of eosophageal inflammation and mucosal integrity</i>	
<i>In vivo</i>	
- Peak eosinophil count/HPF: median;IQR (n = 34)	40; 29 - 80
- ETIS, Ω m: median; IQR (n = 19)	4736; 2417 – 8070
<i>In vitro</i>	
- TER, Ω cm ² : median; IQR (n = 21)	74; 52 - 117
- Fluorescein flux ^a : median; IQ (n = 21)	489; 34 - 1283
- Rhodamine flux ^a :median; IQR (n = 21)	65; 0 - 407

EoE, eosinophilic esophagitis; IQR, interquartile range; TER, transepithelial resistance; ETIS, electrical tissue impedance spectroscopy; ^a Expressed as $\mu\text{mol}/\text{cm}^2/\text{h}$

Table 2. Relationship assessed by multivariable regression analyses between nutrients and food groups, adjusted for age, gender and energy intake (in habitual diet) and number of eosinophils, ETIS *in vivo*, TER and influx of fluorescein and rhodamine *in vitro* (only results with p values < 0.1 are presented).

	Standardized Beta (SE)	p-value	Adjusted explained variance	Nature of the relationship
<i>Relationship between nutrients or food groups and number of eosinophils (n = 34)</i>				
Nutrients				
Protein (g)	0.468 (0.17)	0.066	0.209	unfavorable
Fiber (g)	-0.443 (0.17)	0.044*	0.227	favorable
Iron (mg)	-0.656 (0.17)	0.001*	0.408	favorable
Magnesium (mg)	-0.404 (0.17)	0.055	0.217	favorable
Phosphorus (mg)	0.659 (0.17)	0.001*	0.404	unfavorable
Vitamin B12 (mg)	0.329 (0.17)	0.054	0.218	unfavorable
Food (groups)				
Pasta and rice	-0.361 (0.17)	0.028*	0.248	favorable
Meat and meat products	0.347 (0.17)	0.075	0.203	unfavorable
Soy products	-0.450 (0.17)	0.007*	0.310	favorable
<i>Relationship between nutrients or food groups and mucosal integrity in vivo (ETIS)(n = 19)</i>				
Nutrient				
Retinol Activity Equivalent (RAE)	0.496 (0.23)	0.059	0.153	favorable
<i>Relationship between nutrient or food groups and mucosal integrity in vitro (TER) (n = 21)</i>				
Nutrient				
Potassium	0.571 (0.22)	0.077	0.266	favorable
Food (groups)				
Bread	-0.589 (0.22)	0.059	0.286	unfavorable
Total added fat (margarine, butter, oil, any fat used for cooking)	-0.391 (0.22)	0.093	0.251	unfavorable
Sunflower oil, stir fry oil	-0.499 (0.22)	0.019*	0.370	unfavorable

<i>Relationship between nutrient or food groups and mucosal permeability/integrity in vitro (fluorescein)</i> (n = 21)				
Nutrient				
Linoleic acid	0.405 (0.22)	0.090	0.059	unfavorable
Food (groups)				
Buttermilk/LGG yoghurt drink	-0.716 (0.22)	0.002*	0.417	favorable
Breakfast cereals and other grain products	0.503 (0.22)	0.099	0.050	unfavorable
Bread	0.603 (0.22)	0.089	0.060	unfavorable
Total added fat (margarine, butter, oil, any fat used for cooking)	0.624 (0.22)	0.012*	0.248	unfavorable
Sunflower oil, stir fry oil	0.430 (0.22)	0.083	0.067	unfavorable
<i>Relationship between nutrient or food groups and mucosal permeability/integrity in vitro (rhodamine)</i> (n = 21)				
Food (groups)				
Dairy products	-0.566 (0.22)	0.015*	0.280	favorable
Milk	-0.486 (0.22)	0.051	0.178	favorable
Breakfast cereals and other grain products	0.493 (0.22)	0.093	0.124	unfavorable
Pasta and rice	0.424 (0.22)	0.060	0.164	unfavorable
Total added fat (margarine, butter, oil, any fat used for cooking)	0.484 (0.22)	0.051	0.178	unfavorable
Sunflower oil, stir fry oil	0.735 (0.22)	<0.001*	0.532	unfavorable

*p values < .05